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P/559

2. Patent application number
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21 FEB 1996 **9603699.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if you know it)*

884692001

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

4. Title of the invention

THERAPEUTIC COMPOSITION

5. Name of your agent *(if you have one)*

MRS E J SMITH

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)*

04079422001

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Number of earlier application	Date of filing *(day / month / year)*

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11. I/We request the grant of a patent on the basis of this application.

Signature E. J. Smith Date 20102196

12. Name and daytime telephone number of person to contact in the United Kingdom MRS E J SMITH (0115 949 8774)

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THERAPEUTIC COMPOSITION

This invention relates to a non-effervescent solid dosage form for oral administration, to a process to make said dosage form and to its therapeutic utility.

Ibuprofen, namely 2-(4-isobutylphenyl)propionic acid, is a well known medicament with analgesic, anti-inflammatory and anti-pyretic properties. It is usually sold in the form of racemic ibuprofen (equal amounts of the S(+)-ibuprofen and R(-)-ibuprofen enantiomers). It may also be in the form of the purified form of either enantiomer, especially S(+)-ibuprofen which is acknowledged to be the active form of racemic ibuprofen. Ibuprofen is also available in salt form, for example the sodium salt of ibuprofen. Ibuprofen is available under prescription (eg Brufen (RTM)), primarily for the treatment of painful and anti-inflammatory disorders including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, postoperative pain, post partum pain and soft tissue injuries, generally at doses up to 3200mg per day. Ibuprofen is also available as a non-prescription drug (eg Nurofen (RTM)), primarily for the treatment of symptoms of pain and fever including headache, migraine, rheumatic pain, muscular pain, backache, neuralgia, dysmenorrhoea, dental pain and colds and flu, generally at doses up to 1200mg per day. Ibuprofen tablets usually contain 200mg, 400mg or 600mg ibuprofen.

A major issue in connection with the above disorders is to improve the onset of action of ibuprofen, particularly in the treatment of pain. It is believed that rapid disintegration of a formulation releases the drug into the body and leads to an more rapid onset of therapeutic action compared to a standard dosage form. Accordingly, it is desired to produce a solid dosage form for oral

administration adapted to disintegrate quickly in the stomach and gastro-intestinal tract. It is also preferred that the composition is manufactured by compression on standard tabletting machines to produce a dosage form, with optional granulation and drying stages. However, there are a number of formulation problems associated with providing a rapidly disintegrating solid dosage form containing an ibuprofen medicament. One problem is that in order to achieve a therapeutic dose, solid formulations generally contain a high dose of drug, eg 200mg or 400mg ibuprofen, which thus forms a considerable proportion of the dosage form, ie greater than 35% by weight. Thus, there is a problem to include the ibuprofen medicament, together with the excipients useful to formulate the tablet and the excipients to ensure rapid disintegration, but also to provide a tablet that is both not too large for patient consumption and can be manufactured according to standard processes. Another requirement of such a formulation is that it is capable of being compressed without sticking to the punches of the tabletting machine. Furthermore, the tablet must be sufficiently hard to withstand the rigours of the manufacturing process, for example as encountered during the stage of film coating in a perforated rotating drum, and packaging etc, but must have appropriate disintegration characteristics to ensure rapid release of the drug from the formulation.

We have now found that by incorporating an alkali metal carbonate in the formulation, a tablet of acceptable size can be produced which has a rapid disintegration time and satisfactory hardness.

Previously, it had been found that, in order to produce a tablet of satisfactory hardness, a slight increase in the tabletting compaction pressure in order to improve the hardness led to a significant increase in the disintegration time. Thus, when formulating ingredients, it was difficult to use standard tabletting machine compaction pressures to arrive at an appropriate tablet disintegration time and maintain an acceptably sized tablet of sufficient

hardness. Attempts have also been made to modify the active ingredient by the formation of one or more salts of ibuprofen in-situ in the tablet (eg DE 3922441). We have found that it is not necessary to modify the active ingedient, in fact it is possible to take the active ingredient straight from bulk production of the raw material. Accordingly, we have provided a non-interactive formulation which is stable on storage.

The use of an alkali metal carbonate in combination with a filler and disintegrant component with an ibuprofen medicament to achieve a tablet formulation with satisfactory hardness and good disintegration is surprising. Alkali metal carbonates are soluble materials which have previously been proposed for use in effervescent formulations, for example to react with the acid component in an effervescent couple (see for example WO 94/10994) or to prevent initiation of the effervescent reaction eg during storage. Alkali metal carbonates are not normally used as compressible materials. It was not expected that replacing a proportion of the filler component with a portion of incompressible alkali metal carbonate would not only lead to a tablet having good compressibility properties and hardness but also good disintegration properties.

It was also found that other soluble materials such as sodium bicarbonate, lactose, sucrose, mannitol, sodium citrate and sodium chloride did not yield tablets having the combination of satisfactory compressibility, hardness and disintegration properties and acceptable size, as is achieved by the use of the alkali metal carbonates in a formulation according to the present invention.

Accordingly, the present invention provides a solid non-effervescent dosage form comprising an ibuprofen medicament and a carrier material comprising a filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material further includes an

alkali metal carbonate in an amount such that the dosage form has a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

The use of an alkali metal carbonate allows a reduction in the amount of filler component that would normally be used in a formulation and allows an acceptably sized dosage form to be produced. As indicated above, the inclusion of an alkali metal carbonate also allows a dosage form to be provided which has a satisfactory hardness but also exhibits good disintegration times. Additionally, it is not necessary to include an effervescent couple in a formulation according to the present invention in order to achieve a fast disintegration. Usually, effervescent systems are used in the presence of water (ie the dosage form is added to water prior to ingestion), although very small quantities of acid and alkali may be added to the formulation so that minor effervescence occurs in the aqueous fluids in the mouth and gastro-intestinal tract, which thus facilitates disintegration of the dosage form. The present formulation does not contain any acidic component with which the alkali metal carbonate could react in an effervescent reaction.

The hardness of the solid dosage form may be measured by any machine adapted for this purpose, ie by squeezing the dosage form between two jaws and measuring the force required to break the tablet diametrically. Suitable Hardness Testers are available from Monsanto, Erweka and Schleuniger (manual or automatic operation). The disintegration time may be measured using the method described in the European Pharmacopoeia 1995, Ref V.5.1.1.

The ibuprofen molecule exists in two enantiomeric forms and the term ibuprofen medicament as used herein is intended to embrace the individual enantiomers, especially S(+)-ibuprofen and mixtures thereof in any proportion including a 1:1 mixture which is herein referred to as racemic ibuprofen. The ibuprofen medicament may be also present in the form of any salt or other

derivative of ibuprofen or its enantiomers. If necessary, the ibuprofen medicament may comprise one or more ibuprofen active ingredients such as racemic ibuprofen and S(+)-ibuprofen in combination. However, we prefer that the ibuprofen medicament comprises a single active ibuprofen entity. Representative examples include alkali metal salts, for example the sodium or potassium salts of ibuprofen; alkaline earth metal salts, eg the calcium or magnesium salts of ibuprofen; metal salts, eg the aluminium salt of ibuprofen; amino acid salts for example the lysine or arginine salts of ibuprofen; or amine salts, eg the meglumine salt of ibuprofen. Preferably the ibuprofen medicament is a single salt selected from alkali metal salts, amino acid salts and amine salts. The ibuprofen medicament may also be present in different degrees of hydration. The present invention applies to both anhydrous and hydrated forms, for example the monohydrate or the dihydrate. Greater advantages are obtained in accordance with the present invention by the use of soluble salts of ibuprofen, for example the alkali metal salts such as sodium and potassium, as these materials are poorly compressible. For example, the sodium salt is a flaky, soft and sticky material. It does not lend itself to formulation into a dosage form as it is particuarly difficult to compress. It is also difficult to pre-granulate the sodium salt prior to compression with other excipients into tablets. It thus usually requires an initial treatment stage such as milling, in order to form satisfactory tablets. However, no such pre-treatment of the sodium salt is required in accordance with the present invention. It is thus a further advantage to use sodium ibuprofen taken from a bulk production process to produce the raw material. These soluble ibuprofen salts also have the advantage that, as they are more soluble in an aqueous medium, on release from the formulation they have improved absorption, thus leading to an improved onset of action compared to the substantially insoluble forms of ibuprofen. The sodium salt of ibuprofen is particularly preferred. It has been found that the dihydrate of the sodium salt of racemic ibuprofen is a particularly stable hydrated form, accordingly we prefer to use the sodium salt dihydrate in a compressed dosage form according to the present invention.

The particle size of the ibuprofen medicament should be such as to facilitate the manufacturing process, for example to permit flow during the manufacturing process and thus aiding the compression process. Accordingly, preferably it has a median particle size in the range 25-600μm, preferably 50-300μm, most preferably 150-250μm.

It is desired to have as high a proportion of ibuprofen medicament in the formulation as possible to reduce the size of the solid dosage form. Representative formulations generally comprise ibuprofen medicament to an extent to give 35-90% ibuprofen by weight of the formulation, preferably 35-75% by weight, more preferably 40-60% by weight and most preferably 45-55% by weight. Unit dosages may comprise ibuprofen medicament to an extent of 50mg, 100mg, 150mg, 200mg, 250mg, 300mg, 350mg, 400mg, 500mg and 600mg. Where salts or other derivatives are employed, usually the precise unit doses are chosen to give the equivalent ibuprofen doses set out above, for example 256mg of the sodium salt provides an equivalent dose to 200mg ibuprofen.

The carrier material forms suitably up to 65% by weight of the formulation. Preferred formulations include 25-65% by weight carrier material, more preferably 40-60% by weight and most preferably 45-55% by weight carrier material.

The carrier material comprises a filler component which is used in a sufficient amount to ensure that the formulation containing the ibuprofen medicament is capable of being formed, most preferably by direct compression, into a solid dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes. The filler component is preferably present to an extent of 25-50% by weight of the formulation, more preferably 27-45% by weight, most preferably 30-40% by weight of the formulation. Examples of the filler component include one or

more of cellulose derivatives, starch and derivatives thereof (eg pre-gelatinised starch), soluble sugars (eg lactose, sucrose, dextrin), sodium chloride, calcium phosphate, calcium sulphate cyclodextrin and maltodextrin. Preferably the filler component comprises a cellulose derivative. Examples of suitable cellulose derivatives include methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate and micro-crystalline cellulose. The preferred cellulose derivative used in accordance with the present invention is micro-crystalline cellulose. Further preferably, the cellulose derivative has a particle size above 100μm, preferably in the range 100-150μm.

In preferred formulations the cellulose derivative forms 50-100% by weight of the filler component, more preferably 70-100% and most preferably 90-100% by weight of the filler component. The remainder of the filler component may be formed by other fillers known in the art and as listed above.

In a preferred aspect of the present invention, the filler component is compressible and thus the formulation is capable of compression, preferably direct compression, into a solid dosage form. It will also be appreciated that a directly compressible formulation has advantages as it represents a more efficient tabletting process, namely just mixing the ingredients and then compressing them, thus alleviating the need for the intermediate granulation and drying steps necessary in other tabletting procedures.

The fillers specified above are compressible and may each be used separately or in combination in the amounts indicated above, in accordance with this preferred aspect of the invention.

Accordingly, in a preferred aspect the invention provides a directly-compressed solid non-effervescent dosage form comprising an

ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material further includes an alkali metal carbonate in an amount such that the dosage form has a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

In a preferred aspect of the invention, a formulation capable of compression, preferably direct compression, into a solid composition having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes comprises an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the formulation and the carrier material comprising a filler component, preferably a compressible filler component, in combination with a disintegrating component and an alkali metal carbonate.

Further preferably no liquid (ie water) is added to the formulation in any optional pre-granulation stage or prior to compressison.

The alkali metal carbonate aids the formation of a solid dosage form having the hardness and disintegration characteristics outlined above. The alkali metal carbonate is preferably included in the dosage form in solid form. It is not necessary to dissolve it in a solvent, eg water, prior to any granulation step before compression into a solid dosage form. The properties of hardness and disintegration of the composition are achieved by the presence of the solid alkali metal carbonate in homogenous admixture with the ibuprofen medicament and carrier. It is particularly desired that the particles of the ibuprofen medicament and alkali metal carbonate are intimately mixed. The alkali carbonate does not undergo reaction with any other component of the formulation to form a salt.

The alkali metal carbonate used in accordance with the present invention may suitably comprise sodium carbonate or potassium carbonate either alone or mixed together. Preferably, the alkali metal carbonate comprises sodium carbonate. The alkali metal carbonates may be supplied in varying degrees of hydration for example the monohydrate and dihydrate. Both these forms may be used. However, we prefer to use the anhydrous form. The preferred alkali carbonate for use in accordance with the present invention is thus anhydrous sodium carbonate.

The alkali metal carbonate is present to aid the formulation of the ibuprofen medicament in the dosage form and to provide a solid dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes. Preferably the alkali metal carbonate is present in an amount of 3-20% by weight of the formulation, more preferably 5-15% by weight and most preferably 6-10% by weight of the formulation. The alkali metal carbonate preferably has a particle size in the range of 25-600μm, more preferably 50-100μm.

In a preferred aspect of the present invention, where the filler component comprises 50-100% by weight of a cellulose derivative, the ratio of alkali metal carbonate to cellulose derivative is suitably in the range of 1:1 to 1:20, preferably 1:2 to 1:12, most preferably 1:3 to 1:8 parts by weight. In a further preferred aspect the combined weight ratio of the cellulose derivative and alkali metal carbonate to ibuprofen medicament is 1:10 to 2:1 parts by weight, more preferably 1:4 to 2:1 parts by weight, most preferably 1:1 to 1:2 parts by weight.

The filler component is combined with a disintegrating component. Preferably the filler component selected has disintegrant properties, for example microcrystalline cellulose and/or hydroxypropylmethyl cellulose. However, it may be desirable to specifically incorporate a disintegrant material

in the carrier material. Examples includes one or more of wheat starch, maize starch, sodium starch glycolate, low-substituted hydroxypropylcellulose, alginic acid, cross-linked polyvinylpyrrolidone, magnesium aluminium silicate and croscarmellose sodium. Such disintegrating agents, if used, may form up to 15% by weight of the formulation, for example 1-10% by weight, preferably 5-10% by weight of the formulation.

The tablet may also comprise one or more inert diluents such as lactose, sucrose, mannitol, sodium citrate, sodium chloride and substitutes well known to the person skilled in the art. The inert diluent may be present up to an extent of 50% of the formulation, preferably 0-40%, such as 5-35%.

The formulation may also include a flow aid such as talc or colloidal silicon dioxide, which may preferably be used to an extent of up to 4% by weight of the formulation, for example 0.5-2.0% by weight of the formulation. Lubricants such as stearic acid, sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, calcium stearate, sodium stearyl fumarate or magnesium stearate may also be included in the carrier material. These may be used to an extent of up to 4% by weight of the formulation, for example 0.5-2% by weight of the formulation. Anti-adherents such as talc may further be included in an amount of up to 4% by weight of the formulation, for example 0.5-2% by weight of the formulation. Further optional ingredients which may be added to a tablet composition of the present invention include; intense sweeteners such as aspartame or saccharin; flavour components for example mint such as peppermint; colourants brilliant blue FC1 or C1 food blue (as identified in the standard colour index book).

A solid dosage of the invention may be coated, eg with a sugar or film coating which has minimal effect on the disintegration time. A preferred solid dosage form of the present invention is film coated, such as by spraying tablets with a solution comprising hydroxypropylmethylcellulose and a

plasticiser such as propylene glycol, polyethylene glycol and/or talc in one or more coatings.

A preferred formulation comprises:-

(a) 40-60% by weight sodium salt of ibuprofen (more preferably 45-55% by weight);

(b) 10-50% by weight of a compressible filler, eg micro-crystalline cellulose (more preferably 30-40% by weight);

(c) 5-20% by weight sodium carbonate (more preferably 5-10% by weight);

(d) Up to 10% by weight of a disintegrant, eg croscarmellose sodium (more preferably 5-10% by weight);

(e) Up to 5% by weight of a lubricant, eg stearic acid (more preferably 0.1-2.0% by weight);

(f) Up to 20% by weight of a diluent, eg lactose (more preferably 0-15% by weight);

(g) Up to 2% by weight of a flow aid, eg colloidal silicon dioxide (more preferably 0-1% by weight); and

(h) Up to 5% by weight of an anti-adherent, eg talc (more preferably 0-4% by weight).

In a further preferred formulation the ratio of ibuprofen medicament to carrier material is in the range 1:2 to 2:1 parts by weight, preferably 1:0.5 to 0.5:1 parts by weight, and the ratio of the filler component to alkali metal

carbonate is 5:1 to 1:2 parts by weight. In a more preferred formulation the carrier material comprises 20-80% by weight filler component (more preferably 50-75% by weight), 10-40% by weight alkali metal carbonate (more preferably 10-20% by weight), 10-20% and by weight disintegrant (more preferably 12-18% by weight). Desirably the ratio of the three components (b):(c):(d) above is 2.5-6:1:0.5-2 parts by weight.

A solid dosage form produced in accordance with the present invention may be compressed, preferably directly compressed, to have a hardness in the range of 6.5-15kp, more preferably 10-14Kp. This can be achieved, for example, using standard single punch or rotary tabletting machines having a compression force in the range 100-140MPa.

It will be appreciated by the person skilled in the art that due to the different excipients used in the formulation and varying amounts thereof that for any compression pressure, different formulations will have different hardnesses and disintegration times. Preferred compositions exhibit a hardness of at least 6.5kp and a disintegration time of less than 10 minutes at a compression force above 80MPa. More preferred formulations exhibit a hardness of at least 6.5kp and a disintegration time of less than 10 minutes when compressed at a compression force in the range 100-140MPa such as by a standard tabletting machine, eg a rotary tabletting machine. Such compression pressures include, for example from 100MPa up to 110MPa, up to120MPa or up to 130MPa. Especially preferred compositions exhibit a hardness of at least 6.5kp and a disintegration time of less than 10 minutes when compressed at all pressures in the range 100-140MPa.

As disclosed hereinabove, it is necessary to have a dosage form of appropriate hardness. This is necessary so that the composition retains its integrity and does not crumble and/or break-up during the manufacturing process, the packaging process and transit of the packaged product.

However, it is also necessary to ensure that the dosage form is not too hard that the drug cannot be released from the formulation quickly. Suitable compositions have a hardness in the range 6.5-15kp, preferably 7-12kp, more preferably 8-11kp.

The disintegration time of the tablet formed in accordance with the present invention is less than 10 minutes as measured by a the method described in the European Pharmacopoeia 1995, Ref V.5.1.1 (A. Disintegration Test for Tablets and Capsules). Preferred disintegration times are less than 6 minutes (eg 1-6 minutes), more preferably less than 5 minutes (eg 1-5 minutes) and most preferably 3 minutes or less (eg 1-3 minutes).

Preferred compositions formed in accordance with the present invention may be prepared by standard formulation procedures, such as compression. The final stage of producing the solid dosage form may be preceded by a pre-granulation stage such as initial wet-granulation or initial dry granulation. In the wet granulation stage the ibuprofen medicament is pre-granulated with a binder, such as polyvinylpyrrolidone in a solvent, such as water or a hydrocarbon solvent and then the granules are dried. The granulated material is then mixed with other excipients as necessary and compressed into a solid dosage form. Although the process of the invention may involve a wet-granulation stage, there is no requirement to add a solvent (eg water) at any stage during the manufacturing process and therefore, in a preferred embodiment of the invention, no drying stage is necessary. In a dry pre-granulation stage, certain of the components may be compressed together such as by roller compaction or slugging, and the granules are then mixed with the remaining excipients and compressed into a solid dosage form. The compositions may also be formed by deaggregating powdered ingredients into a container and then blending all of the ingredients to prepare a homogeneous mixture. The mixture may then be compressed to form tablets. This process forms a further aspect of the invention. Thus, there is

provided a process to prepare a rapidly disintegrating, solid dosage form comprising an ibuprofen medicament present to an extent of 35% or more by weight of the dosage form and a carrier material comprising a filler component, preferably a compressible filler component, in combination with a disintegrating component, characterised by including an alkali metal carbonate in the carrier material, and combining the carrier material with the ibuprofen medicament to form a homogeneous solid mixture, optionally with other tabletting excipients, and forming the mixture into one or more solid dosage forms having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes. In a further preferred directly compressed process, the ibuprofen medicament is combined with a compressible filler component and a disintegrant component and the alkali metal carbonate. The other carrier excipients, such as a flow aid and a lubricant, are also added and mixed so that all the powder particles are in intimate admixture, and finally the mixture is compressed.

In therapeutic use the formulations of the present invention are administered orally, thus the therapeutic formulations are presented in solid dosage form, preferably as a tablet. The solid compositions or dosage forms may be used directly for administration to a patient, but are preferably coated with a sugar or film coating, which dissolves substantially immediately the dosage form comes into contact with an aqueous medium. The formulation may also be compressed onto a solid core of another material to form a solid composition with an quick release outer coating. Additionally, the formulation may be present in one or more layers of a multi-layer solid dosage form.

The formulations of the present invention may, if desired, include other compatible pharmacologically active ingredients (for example centrally acting analgesics, eg codeine) and/or enhancing agents. Thus, for example, the formulations may include with any ingredient commonly used in a cough or cold remedy, for example caffeine or another xanthine derivative, and/or

another analgesic, and/or a skeletal muscle relaxant, and/or an antihistamine, and/or a decongestant, and/or a cough suppressant and/or an expectorant.

Suitable antihistamines which are preferably non-sedating include acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, cyproheptadine, dexbromopheniramine, dexchlorpheniramine, diphenhydramine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyrilamine, setastine, tazifylline, temelastine, terfenadine, tripelennamine or triprolidine. Suitable cough suppressants include caramiphen, codeine or dextromethorphan. Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine. Suitable expectorants include guaifenesin, potassium citrate, potassium guaiacolsulphonate, potassium sulphate and terpin hydrate.

Ibuprofen and its derivatives are primarily anti-inflammatory, analgesic and anti-pyretic agents but have also been proposed for other therapeutic uses, eg to treat periodontal bone loss, pruritus, Alzheimer's disease etc. The formulations of the present invention are therefore indicated for use in the treatment of all therapeutic uses for which ibuprofen is effective, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, seronegative arthropathies, periarticular disorders and soft tissue injuries. They may also be used in the treatment of postoperative pain, postpartum pain, dental pain, dysmenorrhoea, headache, migraine, rheumatic pain, muscular pain, backache, neuralgia and/or musculoskeletal pain or the pain or discomfort associated with the following: respiratory infections, colds or influenza, gout or morning stiffness.

In a further aspect the present invention provides a method of obtaining an onset-hastened analgesic and/or anti-pyretic response comprising the

administration of a non-effervescent solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a carrier material comprising a filler component combined with a disintegrating component and an alkali metal carbonate, the dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

In a desired aspect the present invention provides a non-effervescent solid composition produced by compressing a formulation comprising an ibuprofen medicament and a carrier material, the ibuprofen medicament being present in an amount of 35% or more by weight of the formulation and the carrier material comprising a compressible filler component in combination with a disintegrating component, characterised in that the carrier material further comprises an alkali metal carbonate in an amount such that the solid composition has a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

A preferred aspect of the invention provides a non-effervescent formulation comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the formulation and the carrier material comprising a filler component, preferably a compressible filler component, in combination with a disintegrating component characterised in that the carrier material further comprises an alkali metal carbonate in an amount such that the formulation is capable of compression, preferably direct compression, into a solid composition having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

In a further preferred aspect the invention also provides a solid composition having a layer comprising a formulation comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the formulation and the carrier material

comprising a compressible filler component in combination with a disintegrating component characterised in that the carrier material further comprises an alkali metal carbonate in an amount such that the formulation is capable of compression to provide a layer having a hardness in the range 6.6-15kp and a disintegration time of less than 10 minutes.

In yet a further preferred aspect, the invention provides the use of an alkali metal carbonate in a carrier material including a filler component, preferably a compressible filler component, in combination with a disintegrating component, said carrier material being arranged for admixture with an ibuprofen medicament and then for formulation, preferably by compression, into a solid dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes and an ibuprofen content of 35% or more by weight of the dosage form.

The preparation of compressed tablets from formulations of the present invention is illustrated by the following Examples. In the Examples the ibuprofen sodium salt is available from Knoll Pharma, Nottingham, GB; the grades of microcrystalline cellulose are available from the FMC Corporation, Brussels, BE under the tradenames Avicel PH101 and PH102; Croscarmellose sodium is available from the FMC Corporation, Brussels, BE under the tradename Ac-Di-Sol; colloidal silicon dioxide is available from Degussa, Frankfurt, DE under the tradename Aerosil 200; hydrogenated vegetable oil is available from Karlshamn, SE under the tradename Sterotex; hydroxypropylmethyl cellulose 2910 (50CPs) is available from Colorcon, Kent, GB; hydroxypropylmethyl cellulose 2910 (6CPs) is available from Shin-etsu, Japan and the Opaspray is available from Colorcon, Kent, GB.

Example 1

Tablet containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	51.2
Microcrystalline cellulose (PH 102)	35.4
Anhydrous sodium carbonate	5.0
Croscarmellose sodium	7.2
Colloidal silicon dioxide	0.2
Stearic acid	0.5
Magnesium stearate	0.5

The tablets were prepared by screening all the ingredients and blending until an homogenous mixture was obtained. The formulation was then compressed on a single punch tabletting machine using the compression forces given in the tablet below. The hardness of the tablet was measured by recording the diametrical crushing strength when the tablet was broken between the motorised jaws of a Schleuniger hardness tester.

The disintegration time was measured using the method described in the European Pharmacopoeia 1995, Ref V.5.1.1.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	10.4-10.7	5.8
120.0	10.7-11.5	5.4
140.0	10.3-11.2	5.0

Example 2

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium dihydrate	53.1
Lactose NF (Spray Dried)	14.9
Microcrystalline cellulose (PH101)	13.3
Anhydrous sodium carbonate	10.4
Colloidal silicon dioxide	7.5
Stearic acid	0.8

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	8.8-9.2	3.5
120.0	7.2-10.8	3.5
140.0	9.3-11.0	4.5

Example 3

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	51.2
Microcrystalline cellulose (PH101)	12.8
Lactose NF (Spray Dried)	8.0
Anhydrous sodium bicarbonate	20.0
Croscarmellose sodium	7.2
Stearic acid	0.8

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	8.5-9.5	4.3
120.0	9.3-10.4	4.7
140.0	11.1-11.7	4.9

Example 4

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	53.1
Microcrystalline cellulose (PH101)	13.3
Lactose NF (Spray Dried)	14.9
Anhydrous sodium carbonate	10.4
Croscarmellose sodium	7.5
Magnesium stearate	0.8

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	6.6-7.2	4.7
120.0	8.3-10.2	5.4
140.0	8.8-10.1	5.3

Example 5

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	53.1
Microcrystalline cellulose (PH101)	13.3
Lactose NF (Spray Dried)	14.9
Anhydrous sodium carbonate	10.4
Croscarmellose sodium	7.5
Hydrogenated Vegetable oil	0.8

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	6.6-6.9	2.9
120.0	8.5-9.1	3.2
140.0	9.0-10.7	3.7

Example 6

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	51.2
Microcrystalline cellulose (PH101)	12.8
Lactose NF (Spray Dried)	14.4
Anhydrous sodium carbonate	10.0
Croscarmellose sodium	7.2
Talc	3.6
Stearic acid	0.8

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	8.1-8.6	3.5
120.0	9.7-10.5	3.9
140.0	10.7-11.6	4.5

Example 7

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	51.2
Microcrystalline cellulose (PH101)	27.2
Anhydrous sodium carbonate	10.0
Croscarmellose sodium	7.2
Talc	3.4
Stearic acid	1.0

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	7.0-7.4	3.0
120.0	8.1-9.1	3.8
140.0	7.9-10.4	4.5

Example 8

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	51.2
Microcrystalline cellulose (PH102)	35.4
Anhydrous sodium carbonate	5.0
Croscarmellose sodium	7.2
Colloidal silicon dioxide	0.2
Stearic acid	1.0

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	8.4-9.1	3.1
120.0	10.1-10.6	4.1
140.0	12.2-12.7	4.8

Example 9

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	51.2
Microcrystalline cellulose (PH102)	29.6
Croscarmellose sodium	7.2
Anhydrous sodium carbonate	10.0
Colloidal silicon dioxide	1.0
Stearic acid	0.5
Magnesium stearate	0.5

The tablets were prepared as described in Example 1 with the characteristics listed in the table below.

Compression Force (MPa)	Hardness (Kp)	Disintegration Time (min)
100.0	5.8-6.2	2.2
120.0	7.3-7.9	3.3
140.0	9.2-9.8	4.7

Example 10

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	49.7
Microcrystalline cellulose (PH102)	34.3
Anhydrous sodium carbonate	7.8
Croscarmellose sodium	7.0
Colloidal silicon dioxide	0.2
Stearic acid	1.0

The tablets were prepared as described in table 1 to give tablets having a hardness in the range 8-11kp and a disintegration time in the range 4-5 minutes.

The tablet core was coated with the following coatings (% are given of core weight):-

First coat: hydroxypropylmethyl cellulose 2910 (6Cps) (1.016%), talc (0.204%), Opaspray White M-I-7111B (0.336%).

Outer coat: hydroxypropylmethylcellulose 2910 (5-0Cps) (0.437%), Polyethylene Glycol 6000 (0.049%), calcium stearate (0.002%).

Disintegration times of tablets including the coating ranged from 4.17 minutes to 4.75 minutes (therefore showing the film coat had little effect on the disintegration time).

Tablets may also be produced in a similar way to Examples 1-10 above containing sodium ibuprofen in an amount 64mg, 128mg, 192mg, 384mg, 512mg using the same proportions of ingredients.

Example 11

Tablets containing 342.0mg racemic ibuprofen lysine salt
(Ibuprofen equivalent 200mg)

Ingredient	% (wt)
Ibuprofen (dl lysine salt)	68.40
Microcrystalline cellulose (PH102)	20.35
Anhydrous sodium carbonate	5.0
Croscarmellose sodium	5.0
Colloidal silicon dioxide	0.25
Stearic acid	1.0

The tablets were prepared as described in Example 1.

Tablets may also be produced in a similar manner to Example 11 above containing the ibuprofen lysine salt in an amount 171.0mg, 256.5mg and 513.0mg using the same proportions of ingredients.

Example 12

Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	wt (mg)
Ibuprofen sodium salt dihydrate	256.00
Microcrystalline cellulose (PH102)	176.75
Croscarmellose sodium	36.00
Colloidal silicon dioxide	1.25
Stearic acid	2.50
Magnesium stearate	2.50

In the Figures, Figure 1 shows a comparison of the disintegration times of the sodium salt of ibuprofen and the lysine salt of ibuprofen, with and without sodium carbonate as the alkali metal carbonate component. The disintegration time is shown as a function of compaction pressure. The ibuprofen lysine formulation is disclosed by Example 11. The comparison ibuprofen lysine formulation omitted the sodium carbonate but contained the remaining ingredients in the same relative proportions. The ibuprofen sodium Example is disclosed by Example 12 to which 40mg anhydrous sodium carbonate was added. The comparison ibuprofen sodium formulation omitting the sodium carbonate is disclosed by Example 12.

Figure 2 shows a comparison of the disintegration properties of the Example 12 tablets with varying amounts of sodium carbonate (as shown) additionally included in that Example. The disintegration time is shown as a function of the compaction pressure.

It can be seen from Figures 1 and 2 that at standard operating compaction pressures in the range 100-140MPa, the disintegration time of the tablet without sodium carbonate steeply rises reflecting a sharp increase in disintegration time for only a small increase in compaction pressure. The disintegration time vs compaction force gradient for tablets containing sodium carbonate is unexpectedly much more shallow which leads to the processing advantages described herein. In Figure 2 it can be seen that the disintegration times at 100MPa for tablets containing sodium carbonate are less than 300 seconds, whereas omitting this component provides a disintegration time greater than 420 seconds.

Claims

1. A solid non-effervescent dosage form comprising an ibuprofen medicament and a carrier material comprising a filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material further includes an alkali metal carbonate in an amount such that the dosage form has a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

2. A dosage form according to claim 1 wherein the ibuprofen medicament is in the form of the sodium salt.

3. A directly-compressed solid non-effervescent dosage form comprising an ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material further includes an alkali metal carbonate in an amount such that the dosage form has a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

4. A non-effervescent solid composition produced by compressing a formulation comprising an ibuprofen medicament and a carrier material, the ibuprofen medicament being present in an amount of 35% or more by weight of the formulation and the carrier material comprising a compressible filler component in combination with a disintegrating component, characterised in that the carrier material further comprises an alkali metal carbonate in an amount such that the solid composition has a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

5. A composition according to claim 4 wherein the composition is produced by directly compressing the formulation.

6. A non-effervescent formulation comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the formulation and the carrier material comprising a filler component in combination with a disintegrating component characterised in that the carrier material further comprises an alkali metal carbonate in an amount such that the formulation is capable of compression into a solid composition having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

7. A formulation according to claim 6 wherein the filler component is compressible and the formulation is capable of direct compression.

8. The use of an alkali metal carbonate in a carrier material including a filler component in combination with a disintegrating component, said carrier material being arranged for admixture with an ibuprofen medicament and then for formulation into a solid dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes and an ibuprofen content of 35% or more by weight of the dosage form.

9. The use according to claim 8 wherein the ibuprofen medicament is in the form of the sodium salt.

10. The use according to either one or claims 8 and 9 wherein the filler component is compressible and said carrier material is adapted for direct compression with the ibuprofen medicament into a solid dosage form.

11. A method of obtaining an onset-hastened analgesic response comprising the administration of a non-effervescent solid dosage form comprising 35% or

more by weight of an ibuprofen medicament together with a carrier material comprising a filler component combined with a disintegrating component and an alkali metal carbonate, the dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

12. A method according to claim 11 wherein the ibuprofen medicament is in the form of the sodium salt.

13. A method of obtaining an onset-hastened analgesic response comprising the administration of a directly compressed non-effervescent solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a carrier material comprising a compressible filler component combined with a disintegrating component and an alkali metal carbonate, the dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

14. A method of obtaining an onset-hastened anti-pyretic response comprising the administration of a non-effervescent solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a carrier material comprising a filler component combined with a disintegrating component and an alkali metal carbonate, the dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

15. A method according to claim 14 wherein the ibuprofen medicament is in the form of the sodium salt.

16. A method of obtaining an onset-hastened anti-pyretic response comprising the administration of a directly-compressed non-effervescent solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a carrier material comprising a compressible filler component combined with a disintegrating component and an alkali metal carbonate, the

dosage form having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

17. A process to prepare a rapidly disintegrating solid dosage form comprising an ibuprofen medicament present to an extent of 35% or more by weight of the dosage form and a carrier material comprising a filler component in combination with a disintegrating component, characterised by including an alkali metal carbonate into the carrier material and combining the carrier material with the ibuprofen medicament to form a homogeneous solid mixture optionally with other tabletting excipients and forming the mixture into one or more solid dosage forms having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

18. A process according to claim 17 wherein the ibuprofen medicament is in the form of the sodium salt.

19. A process according to either one of claims 17 and 18 wherein the carrier material comprises a compressible filler component and the solid dosage form is prepared by direct compression.

20. A solid composition having a layer comprising a formulation comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% of more by weight of the formulation and the carrier material comprising a filler component in combination with a disintegrating component characterised in that the carrier material further comprises an alkali metal carbonate in an amount such that the formulation is capable of compression to provide a layer having a hardness in the range 6.5-15kp and a disintegration time of less than 10 minutes.

Figure 1

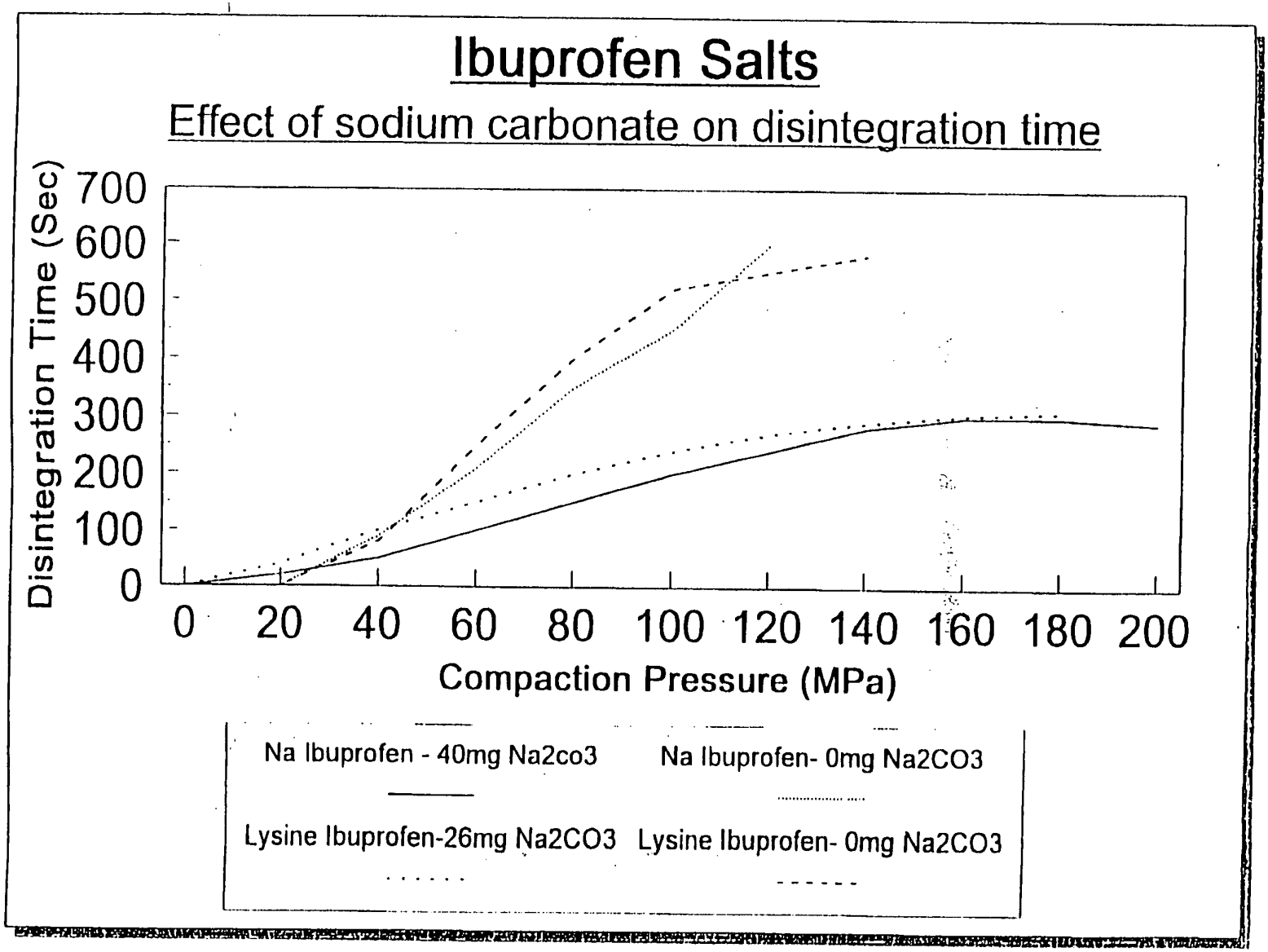
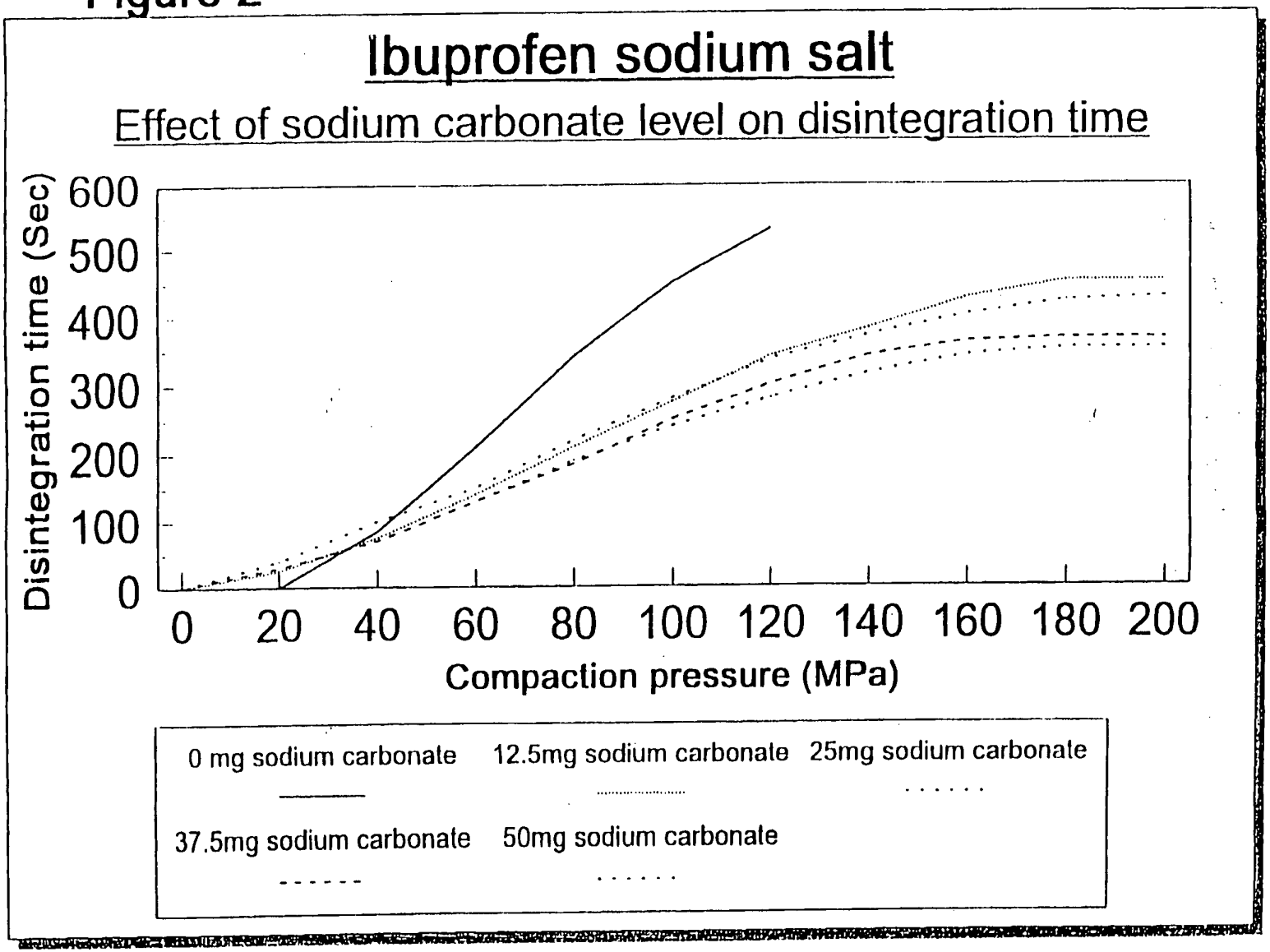

Ibuprofen Salts
Effect of sodium carbonate on disintegration time
Disintegration Time (Sec)
700
600
500
400
300
200
100
0
0 20 40 60 80 100 120 140 160 180 200
Compaction Pressure (MPa)
Na Ibuprofen - 40mg Na2co3
Na Ibuprofen- 0mg Na2CO3
Lysine Ibuprofen-26mg Na2CO3
Lysine Ibuprofen- 0mg Na2CO3

Figure 2


Ibuprofen sodium salt
Effect of sodium carbonate level on disintegration time
Disintegration time (Sec)
600
500
400
300
200
100
0
0
20
40
60
80
100
120
140
160
180
200
Compaction pressure (MPa)
0 mg sodium carbonate
12.5mg sodium carbonate
25mg sodium carbonate
37.5mg sodium carbonate
50mg sodium carbonate